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Association Between Asthma and Coronary Heart Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Airway tightness is a clinical symptom of asthma. It is a diverse syndrome that presents with a range of characteristics. The arteries become inflamed and hardened due to coronary artery disease. Asthma also causes swelling of the airways. Coronary artery disorders are characterized by inflammation and lipid buildup. As a result, numerous writers have reported that asthmatics are more likely to develop cardiovascular diseases (CVD).

Methods: Ten published articles about coronary artery disease and asthma that were released between May 2004 and April 2018 were chosen by the search technique.

Results: The study's pooled analysis revealed a significant correlation between CHD and asthma overall [OR 2.26 (1.45, 3.52), p=0.0003]. The heterogeneity test yielded higher results (I2 = 99%, p<0.00001).

Conclusion: According to this pooled analysis, individuals with asthma have a greater risk of coronary heart disease. Asthma and the incidence of coronary heart disease are positively correlated, according to several earlier research.

Key-words: Asthma, Coronary heart disease, Meta-analysis, Inflammation, Systematic review

INTRODUCTION

Asthma is a long-term inflammatory lung condition. It is a medical disorder when the airway becomes constricted. It has a global frequency of about 4.5% and affects 300 million people [1,2]. According to several studies, asthma is part of a group of illnesses known as heterogeneous syndrome, which exhibits a variety of symptoms [3-5].

It has recently been discovered that several metabolic and inflammatory factors that are shared by obesity, metabolic syndrome, diabetes mellitus type 2 (DM2), cardiovascular disease and mental illnesses may be involved in the causes of adult-onset asthma [5].

Another leading cause of death for people in the US is coronary heart disease [6]. It is a component of heart disease [7]. The arteries become inflamed and hardened due to coronary artery disease. Asthma also causes swelling of the airways. Two typical features of coronary artery disorders are inflammation and lipid buildup [8–12]. As a result, numerous writers have reported that asthmatics are more likely to develop CVD [13–20].

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MATERIALS AND METHODS

Article search- The meta-analysis was conducted using prospective follow-up studies as the basis. Electronic databases, the Cochrane CENTRAL database, medical journals, grey literature (such as abstracts from meetings), trail registries, the World Wide Web, and other pharmaceutical businesses were among the

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sources of evidence we used. Heart disease, coronary artery disease, and asthma were the search terms used. Additionally, a manual selection process was used to choose the highly cited references (Fig. 1).

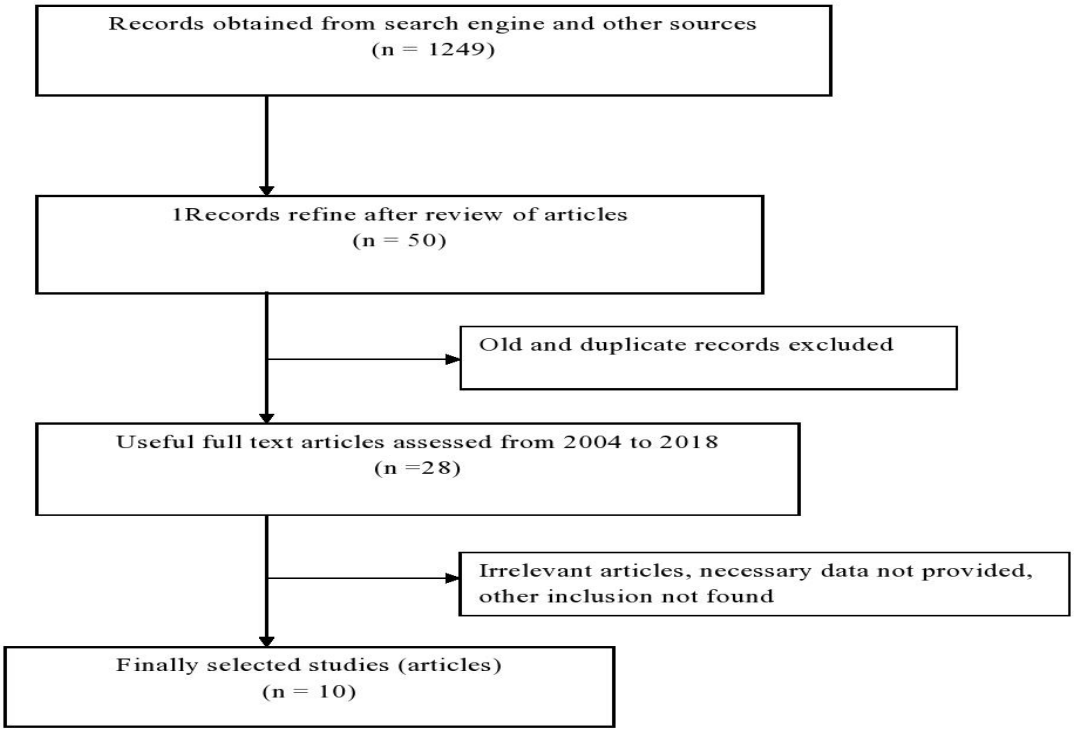

Fig. 1: PRISMA flow diagram

Inclusion criteria

(1) Research published between May 2004 and April 2018 provided the basis for selection.

(2) Articles about heart disease or coronary artery disease with asthma.

(3) Full-text publications were considered.

(4) Articles that were exclusively published in English.

Exclusion criteria- Review articles, research published before 2004, pooled data, articles written in other languages, and articles lacking comprehensive information were all disqualified.

Quality assessment- The Newcastle-Attawa scale was used to evaluate quality. We assessed the included studies' quality, group comparability, and risk factor likelihood.

Statistical Analysis- RevMan 5.3, a program created by Cochrane for systematic reviews and meta-analyses, was used to conduct statistical analysis. Calculating pooled effect sizes, confidence intervals, and heterogeneity metrics like the I2 statistic- which shed light on study variability made possible thanks in large part to this technology.

RESULTS

The search procedure used to find relevant papers for the meta-analysis is depicted in Fig. 1. 1249 records from many search engines were found in the first baseline search. Only 50 articles remained after 1199 were eliminated following the initial abstract screening. Only 28 full-text articles published between 2004 and 2018 were chosen from a total of 50 articles. Upon careful examination of these 28 articles, 18 of them lacked pertinent information. Only ten studies that matched the inclusion criteria were ultimately selected for meta-analysis.

A graphical representation of the findings from several investigations on a common scale is shown in the forest plot in Fig. 2. Each study is denoted by a horizontal line and a square. The study's weight, or sample size, is displayed by the area of the square. Higher precision results from a narrower confidence range with a bigger sample size. 95% CI is shown by the horizontal line. The size of the aggregate effect is shown as a diamond. Additionally, it displays a summary risk estimate together with the associated 95% confidence interval. In contrast to this study, non-significant results are displayed if squares and diamonds meet the null line. According to

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pooled analysis, there was a significant correlation between CHD and asthma overall [OR 2.26 (1.45, 3.52), p=0.0003]. The heterogeneity test yielded higher results (I2=99%, p<0.00001).

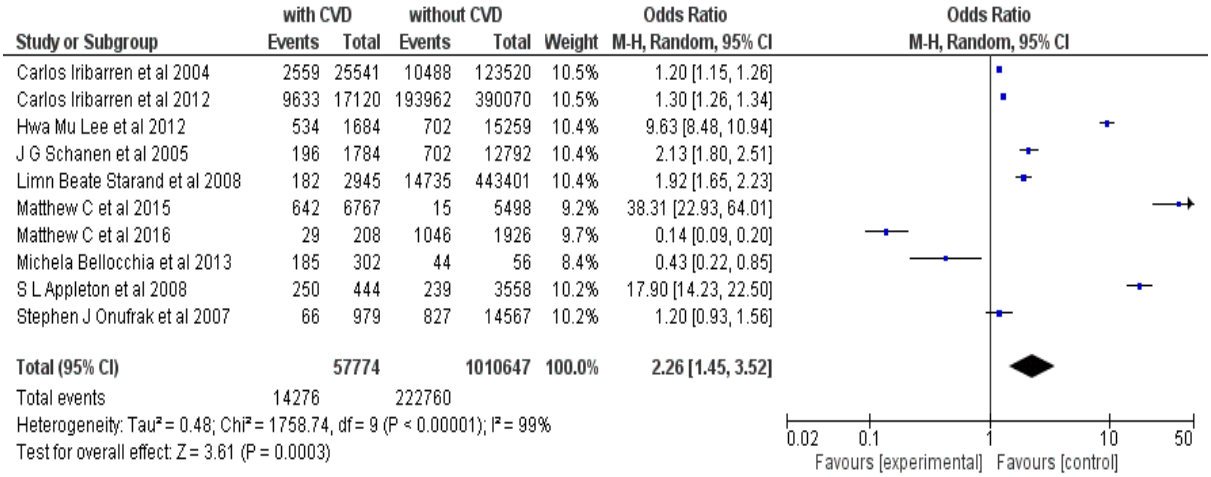

Fig. 2: Forest plot depicting findings from multiple investigations presented on a common scale.

DISCUSSION

Patients with asthma have an increased risk of coronary heart disease, according to this pooled investigation. Asthma and the incidence of coronary heart disease are positively correlated, according to several earlier research. Asthma causes the release of various pro-inflammatory substances that increase vascular inflammation and atherosclerosis, including C-reactive protein, interleukin-6, interleukin-1, tumour necrosis factor-α, and platelet-activating factor [13,21-23]. In addition, a recent study found that asthmatics had higher levels of vascular inflammation than non-asthmatics [24]. Long-term use of asthma medications, such as β-agonists or oral or inhaled corticosteroids, has also been linked in certain studies to an increased risk of CHD [25-28].

Hypoxia and tachycardia brought on by an acute asthma attack can result in CHD symptoms. In addition, the hormone oestrogen controls immune cell migration, allergic inflammation, and the release of pro-inflammatory cytokines and leukotrienes, all of which make asthma worse in women than in men [29,30]. The link between CHD and childhood-onset asthma could be explained by the fact that while environmental irritants or certain allergic reactions can cause childhood-onset asthma, hormones, chest wall stiffening, and cigarette smoking are the main causes of adult-onset asthma. These inherent characteristics may raise the risk of CHD [31-33]. Asthma and CAD have complicated, multifactorial etiopathogenesis.

The majority of CAD is acquired, lifestyle-related, and typically increases after age 40. Atherosclerosis is the primary cause of CAD. High blood pressure, dyslipidemia, diabetes mellitus, smoking, pro-inflammatory activities, obesity, and family history are a few more conventional risk factors [34]. When β2 agonists are administered orally or by inhalation, they can quickly and effectively reverse acute airway blockage brought on by bronchoconstriction. In addition to their positive effects, β2 agonists can have certain serious side effects. Although tachycardia and tremor are frequent side effects, resistance to tremors usually develops. When treatment for an acute asthma attack starts, arterial O_2 may decrease; this could be because of drug-induced pulmonary vascular dilatation [35]. Endothelial damage brought on by mechanical, chemical, and biological stimuli causes atherosclerosis [36]. This leads to an inflammatory response and the production of adhesion molecules because endothelial cells, macrophages, and vascular smooth muscle cells drive monocytes to enter the sub-endothelial region [37].

There are various ways to explain the CAD mechanism. The lipoprotein structure is harmed by free radicals, which are then captured by scavenger receptors found in macrophages and converted into foam cells [38,39]. Second, the pathophysiology of atherosclerosis is also significantly influenced by the renin-angiotensin system, namely by angiotensin II. Through the production of adhesion molecules, inflammatory cytokines, and free radicals, this enzyme results in endothelial dysfunction

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[40]. According to several researchers, atherosclerosis has an autoimmune component [41,42].

Inflammation plays a significant part in the atherogenesis process. The immune system's macrophages, mast cells, and T lymphocytes are the main constituents of atheromatous plaque. These cells use reciprocal impulses to activate one another and take part in a cunning immunological cycle. Mast cells, for instance, can stimulate T-cell activation and activate macrophages [40]. IgE causes degranulation and the release of mediators such as histamine, tryptase, chymase, carboxypeptidase, leukotrienes, prostaglandins, and cytokines when it interacts with allergens on the surface of mast cells and basophils. Th2 lymphocytes produce cytokines (IL-6) and control the activity of mast cells, basophils, and eosinophils. Oedema is caused by symptoms that increase blood vessel permeability, which is brought on by biogenic amines. The smooth muscles of internal organs, such as the bronchi, contract when histamine is present [43].

In a 1998–2011 study with 446346 individuals, Strand *et al.* [44] found that during the follow-up, 2945 deaths were attributable to CVD, 780 to CHD, and 1146 to stroke. Active asthma and no-asthma are the two groups into which they have separated asthma. They discovered that men were more vulnerable than women and that active asthmatics were substantially linked to an elevated risk of CVD patients. According to Tattersall *et al*. [13], there were 223 CVD events throughout follow-up (179 in the non-asthma cohort, 22 in the late-onset asthma cohort, and 7 in the early-onset asthma cohort). More CVD events occur in people with late-onset asthma [45]. Similar findings were made by Tattersall *et al.* [13], who examined inflammatory markers including CRP and IL-6, and discovered that chronic asthmatics had greater levels than both intermittent asthmatics and non-asthmatics. They hypothesized that persistent asthmatics may be at higher risk for CVD due to heightened systemic inflammatory markers. However, more research is required to fully understand this mechanism. Iribarren *et al.* [14] investigated both asthmatic and non-asthmatic subjects. 113,025 participants had 6396 asthma-related events in all coronary heart disease assessments, and the results showed a statistically significant correlation. Women are more strongly associated than males in this study.

There may be a substantial overlap in the inflammatory pathophysiology of CAD and asthma. Asthma inflammation is partly caused by the 5-lipo-oxygenase enzymatic pathway. In the presence of the enzyme 5-lipo-oxygenase, arachidonic acid is transformed into leukotriene A4 in this route, which subsequently transforms into four distinct leukotrienes. These paracrine inflammatory chemicals, known as leukotrienes, are produced by immune cells and may be the cause of both acute and chronic inflammation [9]. Leukotrienes in bronchioles cause smooth muscle and tissue to contract and eosinophils to migrate.

Increase the amount of 5-lipo-oxygenase and leukotrienes found in atherosclerotic plaque [46]. Because plaque instability is caused by elevated levels of the enzyme 5-lipo-oxygenase and leukotrienes, this route is also accountable for CVD events [9,47].

Asthmatics had a lower resting heart rate than controls, albeit the difference was not statistically significant. It implies that those with asthma have a higher parasympathetic drive. Patients with asthma had elevated resting blood pressure, particularly the diastolic blood pressure. According to other researchers who obtained comparable results, this might be because asthmatic patients have higher α-adrenergic drive. Some authors found that asthmatic patients had resting tachycardia [48].

CONCLUSIONS

The prospective association between the incidence of coronary heart disease and asthma is supported by this meta-analysis. We might raise society's awareness of heart disease with the aid of this study. Healthcare providers should regularly monitor asthma and recognize CVD risk factors in this patient population.

Future studies should concentrate on determining viable intervention techniques and investigating the underlying mechanisms that connect asthma and coronary heart disease. Furthermore, to evaluate the effect of asthma treatment on lowering the risk of cardiovascular problems, long-term cohort studies are required.

CONTRIBUTION OF AUTHORS

Research concept- Pallavi Tiwari

Research design- Pallavi Tiwari

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